REMARKS

The above amendment under 37 CFR § 1.114 is in response to the Final Office Action dated March 28, 2006, and further to the Notice of Appeal filed September 19, 2006. Claims 56 and 57 are pending in this case. With the above amendment, claims 56 and 57 have been amended for purposes of clarity and to advance prosecution of this application. It is urged that support for the above amendments can be found throughout the specification as originally filed and that none of the amendments constitutes new matter. In particular, support for the amendments can be found, for example, at page 10, lines 3-4. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter modified and/or removed in a related divisional, continuation and/or continuation-in-part application.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 56-57 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking written description. In particular, the Action asserts that there is no support for a peptide of WT1 that is 249 amino acids or longer but less than full length. The Action also rejected claim 57 as lacking written description due to the recitation of "a Lipid A derived protein."

Without acquiescing to the rejection and solely to advance prosecution, Applicants have amended claim 56 to recite "an isolated polypeptide consisting of amino acids 1-249 of SEQ ID NO:319" and claim 57 to recite "lipid A." Applicants reserve the right to prosecute any subject matter modified and/or removed by this amendment in a related application. Applicants submit that the rejection has been obviated and may be properly withdrawn.

Rejection under 35 U.S.C. § 103

Claim 56 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Chada *et al*. (U.S. Patent No. 5,693,522) or Berzofsky *et al.* (WO 94/21287) in view of Herlyn *et al*. (WO 95/29995). In particular, the Action asserts that Chada *et al*. teach a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are

administered to a patient and that said WT1 peptide is administered with a pharmaceutically acceptable carrier or a non-specific immune enhancer. Further, the Action asserts that the peptide taught by Chada *et al*. encompasses the use of intact WT1. The Action contends that Berzofsky *et al*. teach a method of cancer immunotherapy wherein immunogenic WT1 peptides which stimulate T cell responses are administered to a patient, and that the WT1 peptide is administered with a pharmaceutically acceptable carrier or non-specific immune enhancer to treat WT1 positive Wilms' tumor. The Action admits that neither Chada *et al*. nor Berzofsky *et al*. teaches that the peptide is 249 amino acids or longer but less than full-length WT1. The Action relies on Herlyn *et al*. to overcome this deficiency and asserts that Herlyn *et al*. teach that amino acids 275-429 of WT1 encode a region that has similarity to the Egr1 family and thus, it would not be desirable to induce an immune response directed to this region. Accordingly, the Action asserts that the skilled artisan would have been motivated to combine the teachings of either Chada *et al*. or Berzofsky *et al*. with Herlyn *et al*. in order to avoid generating a potentially deleterious immune response.

Applicants respectfully traverse the rejection and submit that the references, taken for what they teach as a whole, do not obviate the presently claimed invention. As noted above, claim 56 has been amended to recite "a method for enhancing or inducing an immune response to WT1 in a human patient, comprising administering to the patient an immunogenic composition comprising an isolated polypeptide consisting of amino acids 1-249 of SEQ ID NO:319…."

Contrary to the Action's assertions, Chada *et al*. teach the use of "alter[ed] protein encoded by the Wilms' tumor gene" (Abstract, underlining added). At column 8, paragraphs 4-5, Chada *et al*. refer to "an altered gene which causes Wilms tumor" (underlining added):

> Mutations of the Wilms' tumor gene include the insertion of lysine, threonine, and serine between the third and fourth zinc fingers. A wt1 protein which contains such insertions does not bind to the EGR-1 site. A second alternative mutation results in the insertion of about 17 amino acids in the region immediately NH_2-terminal to the zinc finger domain (citations omitted).

> Alterations as described above result in the production of protein(s) containing novel coding sequence(s). The novel protein(s) encoded by these sequence(s) may be used as a marker of tumorigenic cells, and an immune response directed against these novel coding region(s) may be utilized to destroy tumorigenic cells containing the altered sequence(s) or gene(s), which cause Wilms' tumor.

The presently amended claims recite the use of a fragment of a native isoform of WT1. The fragment (amino acids 1-249 of SEQ ID NO:319) does not include either of the alterations called 'novel coding regions' by Chada *et al.*, who propose that immune responses against 'novel coding regions' could be used to destroy tumorigenic cells (see column 8, paragraphs 3-5 of Chada *et al.*, regarding the 3- and 17-amino acid insert alterations to WT1). For the Examiner's convenience, the WT1 sequence is provided below, with amino acids 1-249 of SEQ ID NO:319 underlined and the 3- and 17-amino acid inserts (the 'novel coding regions' of Chada *et al.*) in brackets above the 429 amino acid sequence:

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mgsdvrdlna llpavpslgg gggcalpvsg aaqwapvldf appgasaygs lggpapppap - 60

pppppppphs fikqepswgg aepheeqcls aftvhfsgqf tgtagacryg pfgppppsqa -120

ssggarmfpn apylpscles qpairnggys tvtfdgtpsy ghtpshaaq fpnhsfkhed -180

pmgqqgslge qqysvpppvy gchtptdsct gsqalllrtp yssdnlyqmt sqlecmtwnq -240

 [vaagssssvkwtegqsn]
mnlgatlkg h stgyesdnht tpilcgaqyr ihthgvfrgi qdvrrvpgva ptlvrsaset -300
          ^
sekrpfmcay pgcnkryfkl shlqmhsrkh tgekpyqcdf kdcerrfsrs dqlkrhqrrh - 360

                                [kts]
tgvkpfqckt cqrkfsrsdh lkthtrthtg ekpfscrwps cqkkfarsde lvrhhnmhqr - 420
                                ^
nmtklqlal  -- 429
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Similarly, Berzofsky *et al.* teach using mutated tumor suppressor gene products to induce immune responses against tumors. Berzofsky *et al.* specifically teach generating an immune response against portions of the mutated gene products that actually contain the mutation. For example, at page 4, lines 21-34, Berzofsky *et al.* teach:

> We have now developed a method to immunize with synthetic peptide corresponding to the site of the mutation in the tumor suppressor gene product, p53, to induce CTL that will kill tumor cells endogenously expressing the mutant

> p53 gene, present in a large fraction of lung, breast, and colon cancers, as well as other types of cancers.
>
> Our results show that indeed mutant p53, which is found in a large fraction of cancers of the lung, breast, and colon, and other organs, is a good target for $CD8^+$ CTL and that a peptide spanning a single point mutation can be used to immunize an animal to elicit such CTL (emphasis added).

Additionally, at page 17, lines 11-16, the specification reads:

> We propose, therefore, that eliciting a cytotoxic T-lymphocyte (CTL) immune response to mutated cellular gene products, particularly mutated products of protooncogenes or tumor suppressor genes can give rise to effective tumor therapy (emphasis added).

Further, at page 18, lines 1-7, the specification reads:

> Here we show that an endogenously synthesized mutant p53 protein from a human lung carcinoma can render cells targets for $CD8^+$ CTL, and that these CTL are specific for the mutation, and can be generated by immunization of mice with a synthetic peptide corresponding to the mutant sequence of p53 (emphasis added).

Applicants stress that both references merely list WT1 as a potential protooncogene that could be used to generate an immune response, without demonstrating that WT1 is capable of inducing an immune response, as is disclosed by Applicants. Further, neither reference teaches or suggests using a polypeptide of native, unmutated WT1 consisting of amino acids 1-249 of SEQ ID NO:319, nor do these references teach or suggest that a WT1 peptide consisting of amino acids 1-249 of SEQ ID NO:319 would be capable of effectively eliciting an immune response.

Herlyn *et al.* does not overcome this deficiency. Herlyn *et al.* merely teach the use of a fragment of WT1 consisting of amino acids 1-181 as a tool to generate antibodies in mice. The Action alleges that the reference teaches that it is undesirable to generate an immune

response against amino acids 275-429 of WT1. However, Herlyn *et al.* only mention that this region of WT1 has 50% homology to Egr1 protein family and that the diagnostic antibodies of their invention do not cross-react with this region. Nowhere does Herlyn *et al*. teach or even suggest using a WT1 polypeptide consisting of amino acids 1-249 of the sequence set forth in SEQ ID NO:319 nor compositions comprising such a protein to generate a T cell response against WT1. Herlyn *et al*. disclose no teaching or suggestion that it would be desirable to generate a T cell response to any portion of WT1, let alone amino acids 1-249. Herlyn *et al.* also do not teach or suggest that a T cell response can be generated against amino acids 275-429 of WT1 nor that this would be deleterious. Thus, Applicants submit that the Action employs inappropriate and selective hindsight where the allegation of obviousness is asserted to derive from a reason in the art other than knowledge provided by Applicants' disclosure. *In re Dow Chemical Co*., 837 F.2d 469; 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Absent the teachings of the present application, the documents cited in the Action simply fail to render the claimed invention obvious to the person having ordinary skill in the art, who would have no basis for reasonably believing that the instant methods could be successfully practiced.

In alleging that there would have been motivation to combine the references to arrive at Applicants' method of enhancing or inducing an immune response to WT1 using a WT1 peptide consisting of amino acids 1-249 of SEQ ID NO:319, at best, the Action asserts nothing more than that it would have been "obvious to try." Such an assertion cannot be regarded as a conclusory finding that the claimed invention is obvious, and in fact fails to support a *prima facie* case of obviousness. *In re Eli Lilly & Co*., 902 F.2d 943; 14 USPQ2d 1741 (Fed. Cir. 1990).

Applicants submit that the primary and secondary references, taken individually or for what they teach as a whole, do not teach or suggest the claimed invention. Therefore, Applicants submit that the claimed invention would not have been obvious to the ordinarily skilled artisan at the time of filing. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, the claims are now believed to be in condition for allowance. However, should any further issue require attention prior to

allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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